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Serum adropin levels in patients with migraine

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Abstract
Aim: In this study, we aimed to investigate the relationship between migraine and serum adropin levels.
Material and Methods: This is a randomized control study. The study was conducted for 6 months starting from January 2021. Fifty-four migraine patients were selected for the study as a case group and matched with 35 healthy participants for the control group. We compared serum adropin, high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), total cholesterol (TC) and triglyceride (TG) concentration and body-mass index (BMI) between the case and control groups. In addition, the relationship between migraine disease duration, monthly pain frequency and pain duration, and serum adropin level in the patient group was analyzed.
Results: There was no significant difference between the two groups regarding age, gender, triglyceride, LDL-C, HDL-C, BMI levels and serum adropin levels ($p<0.05$). Also, there was no significant difference in migraine disease duration, frequency of headache (within a month) and headache duration depending on serum adropin levels. A negative correlation was determined between adropin levels and age and BMI ($p<0.05$).
Discussion: Serum adropin concentrations are not associated with migraine in our population. Besides, serum adropin levels decrease with increasing BMI and with age. With this knowledge, however, it is difficult to make a definitive conclusion. Further studies with larger populations are needed.

Keywords
Migraine, Adropin, Body Mass Index, Nitric Oxide

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Introduction

Migraine is a common neurovascular disorder characterized by attacks of severe headache, and autonomic and neurological symptoms. The molecular mechanism of migraine has not been fully clarified yet. The pathophysiology of migraine is correspondingly complex and includes neurogenic inflammation, endothelial dysfunction and oxidative stress [1].

During migraine attacks as a consequence of trigeminovascular activation, nitric oxide (NO) and CGRP, which although transitory, can occur. NO has been implicated in pain processing and is most commonly associated with migraine headache [2]. It was suggested that hemodynamic changes during migraine attacks may be related to alterations in the activity of NO [3]. NO can precipitate the attacks by causing vasodilatation, increased local blood flow, and decreased vascular resistance in cerebral circulation [4].

Adropin is a 4.9 kDa peptide encoded by the Energy Homeostasis Associated gene (Enho) located on chromosome 9 [5]. A variety of organs, including the central nervous system (neurons, neuroglial cells, pia mater, vascular area, Purkinje cells, and granular layer), heart, kidney, liver, pancreas, and human umbilical vein synthesize adropin [6].

Adropin activates vascular endothelial growth factor receptor 2 (VEGFR2) and modulates the expression of endothelial nitric oxide synthase (eNOS) by posttranscriptional stimulation of eNOS protein. Also, adropin increases the endothelial cells proliferation, migration and potential to form capillary-like structures. Recently, it has been found that adropin reduces endothelial permeability [7-9].

As a result of these reports, we aimed to investigate the relationship between migraine, which is well-known to nitric oxide and endotelial dysfunction plays a role in the pathogenesis and serum adropin levels.

Material and Methods

This cross-sectional study was conducted with 89 participants with migraine and a control group of healthy individuals at Elazig Fethi Sekin City Hospital in Turkey January 2021- June 2021. Participants were selected among 18-60 year-old patients with clinical features of migraine and no history of another disease. Patients with no diagnosis of migraine or with peripheral artery disease, active inflammatory disease, autoimmune disease, malignancy, diabetes mellitus, coronary artery disease, severe kidney or liver disease were excluded from the study.

Fifty-four migraine patients were selected as the case group and were matched with 35 healthy participants. We compared serum adropin, high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), total cholesterol (TC) and triglyceride (TG) concentration and body-mass index (BMI) between the case and control groups. In addition, the relationship between migraine disease duration, monthly pain frequency and pain duration, and serum adropin level in the patient group was analyzed.

Measurement of adropin levels in plasma

Venous blood samples were obtained from participants after overnight fasting for at least 10 hours, centrifugated and stored at -80°C until analysis. Serum adropin concentrations were measured using an enzyme-linked immunosorbent assay kit and adropin detection limit range was 0.011-100 ng/ml.

Anthropometric and biochemical measurements

BMI, an assessment of general obesity, was calculated as body weight in kilograms/height in square metres (kg/m^2). Serum TC, HDL-C, LDL-C and TG were measured by enzymatic methods using an autoanalyzer.

Details of the present study were explained to the eligible subjects and written informed consent was obtained.

Statistical analysis

Data analysis was tested using the IBM SPSS Statistics 26.0 (Statistical Package for Social Science) package program. Probability was assessed using a two-tailed P-value of <0.05 to indicate statistical significance. Continuous variables were checked for normality by using the Kolmogorov-Smirnov Normality test. Differences between migraine patients and healthy controls were evaluated with the Mann-Whitney U test for independent non-normally distributed variables, while the independent T-test was used for normally distributed variables. The correlations between parameters to determine test-retest reliability and validity analysis were defined by the Spearman correlation.

Ethical Approval

Ethical approval for the study was obtained from Non-Interventional Clinical Research Ethics Committee of Istanbul Medipol University (Date: 2020-09-04, No: 10840098-772.02-E.43591).

Results

The baseline characteristics of the two groups are shown in Table 1. Compared with the controls, the migraine patients had no significant difference regarding age, TC, LDL-C, HDL-C, TG, BMI and serum adropin levels (p>0.05) as shown in Table 2. We performed the Spearman correlation test to assess the correlations between adropin and clinical characteristics in migraine patients and the control group. As demonstrated in Table 3, serum adropin levels were negatively correlated with age for both groups and the total population (migraine; r = -0,29 (p=0.005), control; r = -0,35 (p=0.037), total population; r = -0,31 (p=0.021)), and BMI only for total population (r = -0,23 (p=0.029)). There was no correlation between serum adropin levels with other variables.

Discussion

To the best of our knowledge, this was the first study to determine the association between serum adropin levels and migraine, migraine attack frequency and migraine attack duration. We could not find any significant results with serum adropin levels between the control group and migraine patients, and there was no association with serum adropin level and

Table 1. Frequency distributions.

Variables	N (%)
Group	
Control	35 (39,3)
Migraine	54 (60,7)
Sex	
Male	24 (27,0)
Female	65 (73,0)

Table 2. Analysis of variables by group (Mean±SD/Median-Range).

	Control n=35(39,3%)	Patient n=54(60,7%)	Total n=89 (100%)	p
Age(year)**	41,06 ± 16,14 / 35-58	35,35 ± 10,74 / 36-40	37,6 ± 13,34 / 36-59	0,071
TC(mg/dl)**	199,66 ± 38,87 / 193-170	182,81 ± 44,43 / 176,5-190	189,44 ± 42,91 / 186-190	0,07
LDL-C(mg/dl)**	121,74 ± 34,61 / 122-137	111,87 ± 33,19 / 109-164	115,75 ± 33,91 / 115-164	0,181
HDL-C(mg/dl)***	52,89 ± 20,32 / 47-117	49,06 ± 10,71 / 47-49	50,56 ± 15,24 / 47-122	0,638
TG(mg/dl)***	156,66 ± 116,41 / 138-566	134,3 ± 70,78 / 126-466	143,09 ± 91,51 / 128-585	0,795
BMI(kg/m^2)**	26,28 ± 4,66 / 26,14-17,81	24,66 ± 3,73 / 24,54-18,51	25,3 ± 4,17 / 25,5-19,33	0,074
Adropin(pg/ml)***	271,85 ± 127,53 / 224,44-461,36	255,98 ± 118,65 / 209,66-449,2	262,22 ± 121,75 / 214,73-461,36	0,559

*<0,05 is significant ** T- Test*** MWU Test

Table 3. Relation of adropin levels and variables-Spearman's Correlation Analysis (r(p)).

	Total n=89(100%)	Control n=35(39,3%)	Patient n=54(60,7%)
Age(year)	-0,29 (p=0,005*)	-0,35 (p=0,037*)	-0,31 (p=0,021*)
TC(mg/dl)	-0,09 (p=0,426)	-0,31 (p=0,070)	0,06 (p=0,669)
LDL-C(mg/dl)	-0,10 (p=0,336)	-0,21 (p=0,226)	-0,02 (p=0,858)
HDL-C(mg/dl)	-0,14 (p=0,182)	-0,29 (p=0,088)	-0,04 (p=0,801)
TG(mg/dl)	-0,03 (p=0,764)	-0,02 (p=0,905)	-0,08 (p=0,557)
BMI(kg/m^2)	-0,23 (p=0,029*)	-0,29 (p=0,093)	-0,19 (p=0,169)
Onset of headache(month)			-0,18 (p=0,199)
Frequency of headache (within a month)			-0,09 (p=0,495)
Headache duration (hours)			-0,18 (p=0,202)

*<0,05 is significant

migraine attack frequency and migraine attack duration.

Migraine affects more than 10% of the world's population, causes substantially more individual morbidity, and creates a significant socioeconomic burden on the individual and society. Despite considerable research into the pathogenesis of idiopathic headaches, such as migraine, the pathophysiological mechanisms underlying them remain poorly understood [10]. A few of the underlying mechanisms are endothelial dysfunction, oxidative stress, vascular inflammation, and hypercoagulability [11]. It is suggested that NO could be an important mediator in the initiation or propagation of a neurogenic cranial vessel inflammatory response that might eventually result in a migraine attack [12]. Nitric oxide is one of the indicators of oxidative stress and causes vasodilation and endothelial dilatation and increases vascular endothelial growth factor (VEGF) [13].

Adropin is a newly discovered regulatory protein encoded by the Enho gene [6]. Adropin appears to have a significant role in energy homeostasis, and may be involved in the metabolic adaptation to fasting and dietary macronutrients [14]. It also might play a role in endothelium by increasing NO secretion and activating eNOS to repair endothelial damage and increasing eNOS expression through the VEGFR2-PI3K-Akt and VEGFR2-ERK1/2 (extracellular signal-regulated kinases 1/2) pathways and inhibition of the Rho/ROCK pathway [6-8]. Although many studies have been conducted in the literature on diseases that are known to play a role in the etiology of endothelial dysfunction such as coronary syndrome, atherosclerosis, diabetes mellitus, obstructive apnea syndrome, erectile dysfunction in coronary artery disease patients [14-19] and low serum adropin levels, there is not any study in the literature with migraine and adropin levels whose pathophysiology is caused by endothelial dysfunction.

In the present study, we have reported a negative correlation between serum concentrations of adropin and BMI and age ($p<0.05$). Zang et al. [20] and Lian et al. [21] found a significant association between BMI and serum adropin levels. In another study by Hu et al., it was shown that BMI was negatively correlated with the serum concentration of adropin in diabetic nephropathy patients. In the same study, no significant correlation of serum adropin with dislipidemia was found [22]. Our study findings are consistent with their study. Furthermore, in Beigi et al.'s study on gestational diabetes mellitus patients showed that there was no significant correlation between serum adropin levels and serum lipid profile, including LDL, HDL, cholesterol and triglyceride concentration, and our study confirmed those results. Although, Beigi et al. found no significant correlation between serum adropin levels and BMI [23].

In many studies in the literature, the association of BMI and serum adropin levels has been established in patients with metabolic diseases such as diabetes, coroner aterosclerosis [14-17]. In our study we found these results without a history of metabolic disease in both the patient and the control group. This can provide a different perspective.

Previous studies have shown a negative correlation between serum adropin levels and age, and this finding was repeated in our study [23,24]. Additionally, Yang et al. found significantly reduced plasma adropin levels in old rats compared to young rats [9]. Also, Celik et al. found a significant correlation between maternal age in gestational diabetes mellitus and cord blood adropin levels [25].

This present study has several limitations. First, the sample size was not sufficiently large to achieve definitive conclusions. Further studies with larger populations are needed. Second, the present study was designed as cross-sectional. Future longitudinal studies are required to determine the causal relationship.

In summary, serum adropin concentrations are not associated with migraine in our population. Besides, serum adropin levels decrease with increasing BMI and with age.

Conclusion

This is the first study to explore the serum adropin levels of migraine patients and the frequency of migraine attacks or the contribution of adropin to the development of migraine, which is a relatively new protein. It is still unclear whether adropin plays a role in the pathophysiology of migraine. Studies with a larger population would be instructive. We think that this study

is beneficial for public health as migraine is the most common headache in the world.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of interest
The authors declare no conflict of interest.

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